DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 3/24/10 has been entered.

Status of Application, Amendments and/or Claims

A new listing of the claims was filed on 3/24/10. No amendments to the claims have been made. The new listing is entered in full.

Claims 70-75 are pending in the instant application.

Claims 73 and 74 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 70-72 and 75 are under consideration, as they read upon the elected species.

Maintained Objections and/or Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-72 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. This rejection was set forth previously and maintained at pg 3-9 of the 10/26/09 Office Action.

For clarity, the rejection is first restated and then Applicants' arguments from the response filed on 3/24/10 are addressed.

The nature of the invention of independent claim 70 is a method of inhibiting vascular growth in a subject suffering from excess vascularization or neovascularization associated with a tumor, comprising administering an amount of a Sonic hedgehog blocking antibody effective to inhibit said vascular growth. The elected species of vascular growth under consideration is a solid tumor that is breast cancer; claim 71 encompasses, and claim 72 is limited to, said species. Claim 75 limits the method to one wherein the antibody inhibits angiogenesis.

The term "vascular" refers to vessels that circulate biological fluids such as blood or lymph; therefore "vascular growth", "vascularization", and "neovascularization" include vasculogenesis and angiogenesis of blood and lymph vessels. With respect to blood vessels the relevant art teaches, "[i]n vasculogenesis, endothelial cells are differentiated *de novo* from mesodermal precursors, whereas in angiogenesis, new blood vessels are generated from pre-existing ones. Vasculogenesis occurs only during embryonic development and leads to formation of a primary capillary plexus. In angiogenesis, new capillaries form and remodel by budding (sprouting), splitting (intussusception) and fusion (intercalated growth), producing a juvenile vascular system and then a mature one" (pg 2013 of Cohen Jr, 2006. American Journal of Medical Genetics. 140A: 2013-2038; cited previously). However, other teachings in the relevant art suggest that vasculogenesis may also contribute to blood vessel formation in adult mammals; however, the role of this contribution is not well-characterized (see pg 157 of Ribatti et al. 2001. Mechanisms of Development. 100: 157-163; cited previously).

The scope of claim 70 encompasses treatment of any subject suffering from excess vascularization or neovascularization associated with a tumor. The specification teaches that conditions of "excess vascularization" or "neovascularization" include "a variety of solid tumors such as breast cancer" and "hemangiomas in infancy" (pg 28, lines 11-12). The specification further teaches, "abnormal vascular growth such as

occurs in tumors", hemangiomas, angiofibromas. (pg 2, lines 22-23). Thus, claim 70 (and dependent claim 75) broadly encompass treatment of any tumor of any type of tissue, including both malign (e.g., breast cancer, prostate cancer, lung cancer, pancreatic cancer, colon cancer) and benign (e.g., hemangioma of infancy, angiofibroma, adenoma, lipoma). Of these, the elected species under consideration is a solid tumor (claim 71) that is breast cancer (claim 72).

The specification as originally filed provides minimal guidance to the skilled artisan with respect to practicing the claimed method with any of the envisioned tumors including the elected species. The specification does not provide any *in vivo* working examples of treatment of a condition of "excess vascularization or neovascularization" with a "Sonic hedgehog blocking antibody". Furthermore, the specification does not provide any *in vitro* models that correlate with *in vivo* treatment. Although Applicants need not to have actually reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02).

Examples 3-6 of the specification provide teachings that are very limited in relation to the claimed inventions. Example 3 teaches that exogenous Sonic hedgehog (Shh) protein added to explant culture can "stimulate hematopoiesis in the epiblast mesoderm" in place of visceral mesoderm (pg 44, lines 6-20). Hematopoiesis was assessed by measuring ε-globin (see description of Figure 9 on pg 8), which the specification teaches as a marker of erythroid (red blood) cell formation (pg 28, lines 20-21). Example 3 further teaches that Shh or Indian Hedgehog (Ihh) proteins stimulate proliferation of cultured adult hematopoietic stem cells isolated from bone marrow. Example 4 demonstrates that "Shh blocking antibody" reduces ε-globin expression in cultured murine whole embryo (pg 48). Example 5 demonstrates expression of *patched* and *Gli* (genes that encode hedgehog signaling pathway components) that was "substantially exclusive in the yolk sac mesoderm" (pg 48). Example 6 states that, "both *Indian hedgehog* and *BMP-6* are expressed in early visceral endoderm." Based on these results, the specification asserts that hedgehog proteins "have utility in regulating hematopoiesis and vascular growth in the adult animal" (pg 13, lines 24-25). However,

these examples in the specification are all related to *in vitro* hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. As taught in the specification, "[i]n contrast to vascular growth, hematopoiesis is normally a continuous process throughout the life of an adult" (pg 2, lines 26-27). There are no examples related to stimulation or inhibition of vascular growth in either an embryo or an adult in either normal or diseased individuals with a solid tumor.

The post-filing date art does support a role for the hedgehog pathway in the growth and angiogenesis of a certain subset of solid tumors. For example, Nagase et al teaches, "Shh signalling has been implicated in the development of several malignancies including basal cell carcinoma of the skin, lung cancer and medulloblastoma ... and it is possible the Shh mediates tumor angiogenesis ... Hh signaling may be enhanced, stimulating tumour angiogenesis" (pg 74 of Nagase et al, 2008. Angiogenesis, 11: 71-77; cited previously). Yamazaki et al, 2008 teaches (with respect to pancreatic tumors) "[o]ur results imply that SHH secreted from cancer cells facilitates tumor growth not only by stimulating proliferation of cancer in an autocrine manner but also by promoting angiogenesis through EPC activation in a paracrine manner" (pg 1137 of Yamazaki et al, 2008. Cancer Sci. 99(6): 1131-1138; cited previously). As such, the instant claims encompass inhibition of excess vascularization or neovascularization associated with a tumor that occurs by (1) directly, by blocking the Shh stimulating paracrine vascular growth; and/or (2) indirectly, by blocking the Shh stimulating autocrine tumor growth, which in turn prevents additional vascular growth associated with the tumor.

However, the post-filing date art makes it clear that many solid tumors do not include dysfunctions that lead to Shh overexpression. For example, Thievessen et al (2005) teaches, "our data suggest that hedgehog pathway is weakly active in normal adult urothelial cells and of limited importance in TCC [transitional cell carcinoma]" (abstract) and "the hedgehog pathway has been reported to become activated in small cell lung cancer, but not in other histological types of lung cancer" (pg 376 of Thievessen et al, 2005. Journal of Cellular Physiology. 203: 372-377; cited previously). Furthermore, even in small cell lung cancer, Watkins et al observed that only 50% of

primary tumors (5 of 10) expressed the Sonic hedgehog protein (see page 314 of Watkins et al, 2003. Nature. 422(6929): 313-7 plus 2 pages of Supplementary material; cited previously; see also Supplementary panel a, the legend for which states "The SCLC case demonstrates [sic] variable co-expression of Shh and Gli1 in tumor cells"). Furthermore, the relevant art teaches that "the published results on primary human colon cancers are also confusing. Some authors, but not others detected increased levels of Hh pathway members during colon cancer progression. Moreover, the expression of Ihh and Gli1 were shown to be decreased during colon cancer progression in recent publications" (see pg 2626 of Chatel et al, 2007. Int J Cancer. 121: 2622-2627; cited previously). With respect to the elected species of solid tumor associated with breast cancer, Thomas et al (2011) teach that one inflammatory breast cancer (IBC) cell line overexpresses SHH, but other IBC, non-IBC, and non-cancerous cell lines do not (see Figure 1B of Thomas et al, 2011. British Journal of Cancer. 104: 1575-1586). Furthermore, U.S. Pre-Grant Application Publication 2004/0110663 (a publication of application 10/652,298; cited on the IDS filed 10/22/07) reports that high levels of *gli-1* expression (as compared with "non-proliferative" cells) are found in some tumors of the prostate, lung, and breast ("8 out of 18 breast cancer samples showed substantially increased gli-1 expression. 7 out of 11 lung cancer samples, 11 of 19 benign prostatic hypertrophy samples (BPH), and 6 out of 15 prostate cancer samples all showed strong gli1 expression"; ¶ 759 of the '663 publication). The '663 publication further reports that the growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by the Sonic hedgehog blocking antibody 5E1 (Figure 54; ¶ 848). Thus, the art provides evidence that many tumors of different tissues do not include activation of the hedgehog signaling pathway such that Shh is overexpressed. This supports the general concept that different conditions of abnormal vascular growth in adult subjects (e.g., solid tumors from different patients) does not necessarily involve expression of the same angiogenic molecules. This variable expression "not only among different tumour types, but also with the same tumour" has also been observed with vascular endothelial growth factor (VEGF), another molecule associated with

angiogenesis (pg 394 of Ferrara et al. 2004. Nature Reviews Drug Discover. 5(3): 391-400; cited previously).

Based on limited working examples showing a role of the Sonic hedgehog protein in *in vitro* hematopoiesis, the instant specification asserts that antagonists of Sonic hedgehog signaling, such as a Sonic hedgehog blocking antibody, can be used to treat excess vascularization or neovascularization, such as the elected species of solid tumor that is breast cancer. However, the instant specification contains no recognition that aberrant Shh expression is associated only with certain subset of tumors. Instead, the instant specification directs the skilled artisan to treat any tumor, including any solid tumor that is breast cancer with a Sonic hedgehog blocking antibody. However, in view of the teachings of the post-filing date art, the skilled artisan would predict that a breast cancer tumor that does not overexpress the Sonic hedgehog protein would fail to be inhibited by administration of a Sonic hedgehog blocking antibody. What is missing from the specification is the critical guidance to first determine that the solid tumor is associated with misregulation of the Sonic hedgehog signaling pathway that results in Shh overexpression. In view of the lack of guidance provided by the specification and the prior art the skilled artisan could not practice the claimed method without undue experimentation.

Applicants' arguments (3/24/10, pg 3-8) as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

In section A of the 3/24/10 response (pg 3-4), Applicants argue that Example 4 demonstrates that a Shh blocking antibody inhibits vascular growth and hematopoiesis in whole mouse embryonic cultures, and that this example in combination with the level of skill in the art enables the skilled artisan to practice the claimed method. Applicants further argue that the enablement requirement does not turn on the presence or absence of working examples; Applicants point to MPEP 2164.02. Applicants argue that the claimed method relies on targeting the vascular growth accompanying tumors rather than tumor cells *per se*, "thereby making the claimed method beneficial across a range of tumors of diverse etiology" (pg 4). Applicants argue that because inhibition of

vascular growth was known in the art at the time of filing to beneficial for treatment of tumors, the specification need not provide a detailed description of the information; Applicants point to MPEP 2163(II)(A)(2). Applicants further argue that the skilled artisan "would have no difficulty in understanding how to use the claimed method" because the prior art teaches methods for treating breast cancer patients by administering an antibody therapeutic. Applicants point to Valone et al (1995) and Weiner et al (1995) in support. Applicants argue that these references teach the skilled artisan several therapeutic antibody treatments, including formulation and dosages for administration and analyzing efficacy.

These arguments have been fully considered but are not found to be persuasive. As set forth previously, Example 4 demonstrates that "Shh blocking antibody" reduces ε-globin expression in cultured murine whole embryo (pg 48). It is maintained that ε-globin expression is a marker for hematopoiesis rather than vascular growth, and hematopoiesis is a different molecular process from vascular growth. Thus, it is maintained that there are no examples in the specification related to stimulation or inhibition of vascular growth in either an embryo or an adult in either normal or diseased individuals with a solid tumor. Although Applicants need not to have actually reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). Furthermore, the connection between inhibition of vascular growth and therapeutic treatment of tumors is not disputed; however, it is disputed that vascular growth of tumors necessarily involves Shh activity such that blocking such activity would inhibit the vascular growth. MPEP 2163(II)(A)(2) provides guidance concerning the written description of an invention; the instant claims are not subject to a written description rejection. The relevant art provides evidence that tumor-associated angiogenesis is a paracrine effect dependent on secretion of Shh from the tumor (see the teachings of Yamazaki et al, 2008 cited above). There is no evidence in the relevant art that Shh plays a role in tumor angiogenesis independent of tumor expression of Shh. Furthermore, the relevant art teaches a distinction between vasculogenesis in

embryonic development and angiogenesis in later tissues (see citation above from Cohen et al, 2006).

What is missing from the specification is the critical guidance that successful treatment first requires determining that the solid tumor is associated with misregulation of the Sonic hedgehog signaling pathway that results in Shh overexpression. The references of Valone et al (1995) and Weiner (1995) do not address this issue. Instead they are directed to treatment of breast cancer using antibodies that act by a completely different mechanism than by blocking Sonic hedgehog activity. Valone et al and Weiner et al each teach a bispecific antibody that simultaneously binds a tumor antigen and a receptor for IgG, to active immune effector pathways against the tumors. Valone et al teach that such an approach is necessary because monospecific antibodies for tumor antigens "have had little direct therapeutic effect" (pg 2281). Thus, the studies described by Valone et al and Weiner et al to show the efficacy of the bispecific antibodies does not provide guidance to the skilled artisan when practicing the claimed invention using a Sonic hedgehog blocking antibody. Furthermore, these studies show the type of necessary and significant experimentation to demonstrate efficacy of a breast cancer treatment that is lacking from the instant application.

In section B, part (i) of the response (pg 5), Applicants argue that the skilled artisan would have recognized that the working example concerning ε-globin relates to both hematopoiesis and vasculogenesis, because "embryonic hemoglobin was used as a marker for vasculogenesis at the filing date of the pending application". In support, Applicants point to Thompson et al (1987; Exhibit C) as teaching analysis of embryonic hemoglobin content of the chick chorioallantoic membrane as an assay for assessing angiogenesis in embryonic tissue, specifically that an increase in hemoglobin content after histamine application is consistent with an increase in vasculature.

These arguments have been fully considered but are not found to be persuasive. The teachings of Thompson et al differ significantly from the working example in the instant specification concerning ε-globin (Example 4). Thompson et al uses chick chorioallantoic membrane (CAM), which is significantly different from the cultured whole mouse embryos used in Example 4 in both species and structure. Furthermore,

Thompson et al engage in experimentation to determine a consistency between the increase in globin and vascularity following addition of histamine to the CAM. Such experimentation, showing a correspondence between globin content and vascularity in response to histamine, is absent from Example 4. The prior art teaches, specifically with respect to a murine system, that "primitive erythropoiesis does not require the formation of an intact vascular network" (pg 162 of Palis et al, 1995. Blood. 86 (1): 156-163; reference CL4 on the 4/13/11 IDS). Furthermore, the relevant art teaches a distinction between markers of primitive erythroblasts and vascular endothelial cells. Dyer et al (2001. Development. 128: 1717-1730; reference BC on the 2/3/04 IDS) teaches a distinction between primitive hematopoietic (ε- and β-*globin*, *Gata1* and *Cd34*) and endothelial (*Vezf1*, *Pecam* and *Flk1*) markers in mouse embryo. In murine tissue, hematopoiesis (erythropoiesis) is not necessarily regulated in the same manner as vascularization, and thus Thompson et al do not demonstrate that Ɛ-globin was routinely used in the art as a marker of vascularity in the system used in Example 4. While the specification indicates that the Examples in the specification relate to both hematopoiesis and vasculogenesis, it is maintained that this is speculative as there is insufficient evidence that ε-globin is considered a marker of embryonic vasculogenesis in the relevant art at the claimed priority date.

In section B, part (ii) of the response (pg 6), Applicants argue that post-filing date art supports a link between Shh signaling and vascular growth. In support, Applicants point to Soletti et al (2009; Exhibit D) as showing that microparticles "harboring Shh peptides were sufficient to induce angiogenesis in vitro through the upregulation of various pro-angiogenic factors".

These arguments have been fully considered but are not found to be persuasive. The teachings of Soletti et al have been fully considered but are not sufficient to overcome the rejection. The rejection of record acknowledges that Shh can stimulate paracrine vascular growth; Soletti et al provide in vitro evidence showing that microparticles (plasma membrane fragments) comprising Shh can stimulate vascular growth. Soletti et al further teach that upregulation of Shh is associated with particular tumors and that tumors shed microparticles comprising Shh (pg 580, right column).

Soletti et al does not provide any evidence that tumors lacking misregulation of Shh expression can be treated with Shh blocking antibody. Thus, the teachings of Soletti et al are consistent with the rejection of record.

In section B, part (iii) of the response (pg 6-7), Applicants argue that embryonic cultures such as those used in Example 4 are commonly used to study angiogenesis in later development, including tumor associated angiogenesis. In support, Applicants point to Allen et al (1993; Exhibit E) and Ribatti et al (1996; Exhibit F).

These arguments have been fully considered but are not found to be persuasive. The teachings of Allen et al and Ribatti et al have been fully considered but are not sufficient to overcome the rejection. The teachings of Allen et al and Ribatti et al are directed to the CAM assay and not to the assay used in Example 4, which employs cultured whole murine embryo. Furthermore, Ribatti et al teach that CAM is one of the "most reliable" assays of angiogenesis. Thus, teachings directed to CAM do not speak to the use of other assays, and instead suggest that such assays are less reliable. Furthermore, as described above, the assay used in Example 4 is directed only to hematopoiesis and not to vasculogenesis, and as set forth previously, the hemoglobin subunit ε-globin is expressed only in the embryonic yolk sac and is replaced by other subunits in fetal and adult tissues. Ribatti et al and Allen et al do not mention the use of ε-globin in embryonic tissues in any context, including as a marker of vasculogenesis in adult tissues. Ribatti et al is a review of the state of the art of CAM as a model of angiogenesis just before (1996) the claimed priority of the instant invention (2/10/97), so the skilled artisan at the time would have expected this review to describe this use if it was routine in the art.

In section C of the response (pg 7-8), Applicants state that they "maintain the arguments put forth in the June 25, 2008 and April 13, 2009 Responses [sic], that the claimed invention is not based on necessarily modulating hedgehog signaling in tumor cells, but rather on inhibiting enhanced vascular growth ... accompanying a solid tumor" (pg 7). Applicants further argue that it is well understood in the art that angiogenesis is crucial for growth of many malignant solid tumors, even if Shh overexpression is not observed in all tumors. Applicants argue that the specification provides teachings such

that the skilled artisan could administer Shh blocking antibody to inhibit block Shh signaling and thus inhibit angiogenesis in "developing solid tumors - regardless of whether the tumor itself is characterized by misregulation in hedgehog signaling" (pg 8).

These arguments have been fully considered but are not found to be persuasive. It is maintained that in view of the relevant teachings of the post-filing date art (cited in the rejection above), administration of a Sonic hedgehog blocking antibody would not result in treatment of a solid tumor unless the tumor exhibits overexpression of the Sonic hedgehog protein. It is acknowledged that determination of the specific mechanism of dysregulation leading to such overexpression is not needed, but determination of such overexpression is necessary to identify those tumors that can be successfully treated with the blocking antibody. It is not disputed that inhibition of angiogenesis is a widely acknowledged strategy in the art for tumor treatment. However, Applicants provide no evidence that a hedgehog antagonist such as a blocking antibody can inhibit the vascular growth associated with the many solid tumors in which the Sonic hedgehog antibody is not overexpressed. The relevant art provides evidence that tumor-associated angiogenesis is a paracrine effect dependent on secretion of Shh from the tumor (see the teachings of Yamazaki et al, 2008; cited above). There is no evidence in the relevant art that Shh plays a role in tumor angiogenesis independent of tumor expression of Shh.

Applicants further argue (pg 8) that the fact that the 5E1 antibody did not inhibit the growth of the solid tumor produced by the SW480 cell line does not address the question of whether the Sonic hedgehog antibody inhibited vascular growth associated with the tumor. Applicants refer to arguments previously submitted to “support the conclusion that the experiment provided in the ‘663 publication is simply not relevant to assessing enablement of the claimed methods because the experiment did not examine angiogenesis or otherwise report data to allow conclusions regarding any effect (or lack of effect) on angiogenesis" (pg 8).

These arguments have been fully considered but are not found to be persuasive. Here, Applicant refers to arguments presented previously. These arguments have been addressed previously (pg 13-14 of the 10/26/09 Office Action), and are not sufficient to

overcome the rejection for the reasons set forth previously. In summary, Applicants argument that the SW480 strain can grow without corresponding vascular growth is a hypothetical argument unsupported by evidence, and goes against he accepted model of solid tumor growth as set forth at page 60 of the instant specification. Thus, it is maintained that the results described in the '663 publication (that growth of a xenograft of non-hedgehog expressing colon cancer cell line SW480 is not inhibited by the Sonic hedgehog blocking antibody 5E1) is a further example of solid tumors that do not include dysfunctions that lead to Shh overexpression, and thus are not treatable by a Shh blocking antibody.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Zachary C Howard/
Examiner, Art Unit 1646